Docket No. 515-4183

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT OPERATION

Applicants: **Maurizio Valleri & Alessandro Tosetti**

Serial Number: **09/463,586**

Filing Date: **April 24, 2000**

Examiner: Pulliam, Amy E.

Art Unit: 1615

Title: **PHARMACEUTICAL COMPOSITION CONTAINING VITAMIN D AND CALCIUM, THEIR PREPARATION AND THERAPEUTIC USE**

New York, NY 10036
September 2, 2003

Mail Stop Appeal Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-8 and 13-19 by the Primary Examiner.

I hereby certify that this paper or fee is being deposited with the United States Postal Service as first class mail on **September 2, 2003** in an envelope addressed to:

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(1) Real Party in Interest

The real party in interest is Menarini International Operations Luxembourg S.A.

(2) Related Appeals and Interferences

An Appeal Brief was filed in the present application on May 14, 2002, subsequently the final rejection was withdrawn by the Examiner, and. Then, an Office Action allowing Claims 9-12 and rejecting Claims 1-8 and 13-19 was mailed on July 30, 2002. Applicant then mailed an Amendment, which was filed on December 9, 2002. Lastly, the present final rejection was mailed on March 26, 2003 and Applicant filed a Notice of Appeal on June 30, 2003.

(3) Status of Claims

Claims 1-8 and 13-19 have been finally rejected. Claims 9-12 have been allowed.

(4) Status of Amendments

No Amendment was filed in response to the final rejection.

(5) Summary of Invention

The present invention refers to pharmaceutical compositions containing Vitamin D and a calcium salt, the process for their preparation, and their use in the treatment of pathological forms involving loss of bone tissue in the elderly, such as osteoporosis, as well as the prevention of illnesses linked to calcium metabolism in the elderly, such as those leading to fractures of the proximal femur or other non-vertebral fractures.

(6) Issues

Do the disclosures of Meignant et al., FR-A-2 724 844 in view of Andob et al., United States Pat. No. 5,576,021 OR Tovey, United States Pat. No. 4,493,822 OR Remington's Pharmaceutical Sciences, render claims 1-8 and 13-19 unpatentable under 35 U.S.C. §103?

(7) Grouping of Claims

The grounds for rejection are to be considered separately. Claims 1-8 and 13-18 are to be considered together. Claim 19 is to be considered separately.

(8) Argument

Claims 1-8 and 13-19 were rejected under 35 U.S.C. §103 as being unpatentable over Meignant et al., FR-A-2 724 844 in view of Andob et al., United States Pat. No. 5,576,021 OR Tovey, United States Pat. No. 4,493,822 OR Remington's Pharmaceutical Sciences.

This rejection is in error for the following reasons.

The Examiner applied Meignant as describing the combination of calcium and Vitamin D within the range claimed by the applicants. The amount of calcium/Vitamin D disclosed by Meignant is not within the applicants' claims because the applicants' claims require a minimum amount of 500 I.U. of Vitamin D with a minimum amount of 1g of calcium. In addition, the claims point out that a ratio of 1-2g of calcium to 500 to 1000 I.U. of Vitamin D is present.

Meignant describes the use of 4mg or 400 I.U. of Vitamin D and 0.5g of calcium and does not disclose any composition having more than 400 I.U. of Vitamin D. Thus, the ratio of 0.5g of calcium/400 I.U. of Vitamin D is described by Meignant. However, the present claims point

out a minimum amount of 500 I.U. of Vitamin D. For this reason, the ratio of 0.5g of calcium/400 cannot fall within a claim which requires a minimum of 1g of calcium and a minimum of 500 I.U. of Vitamin D. If 2g of calcium is used according to the applicant's claims, it must be used with 500 to 1000 I.U. of Vitamin D. If the ratio of 2g/1000 I.U. of Vitamin D is reduced to 1g/500 I.U. of Vitamin D, the maximum value of 0.5g/400 I.U. of Vitamin D as disclosed by Meignant is substantially below the value of claim 1.

Meignant refers to a pharmaceutical composition which must be prepared in a "humid environment" (see claim 4, page 11). Further, it is well known in the art that the use of a humid process of preparation can leave traces of humidity in the granules, which may result in a degradation of the Vitamin D, which undergoes spontaneous oxidation. Claim 1 was amended to exclude the possible presence of water in the product by pointing out that the composition "consists essentially of" the recited components. This further distinguishes the subject matter of claim 1 from Meignant.

The preferred calcium salt is calcium phosphate and its analogs, i.e. compounds that have a high content of calcium but are insoluble. The calcium salts used in the prior art were granulated to avoid poor flow characteristics. This made them unsuitable for processing using ordinary high output machines. However, when used in suspensions, these granules increased the rate of sedimentation causing a "sand effect", thereby decreasing the uniformity of the distribution of the active ingredients within the product. In order to make pharmaceutical compositions for oral use that do not present a "sand effect" it is necessary to identify the exact additives that show acceptable texture, and at the same time allow for an industrial preparation of the composition. Therefore, it was necessary to utilize binders that would be effective in a dry environment,

with high concentrations of an insoluble calcium salt such as calcium phosphates. These conditions and binders are not disclosed in Meignant.

The Andoh patent describes the use of a granulation technique in making tablets. Various binders are described but there is no mention of the problems that arise when polyvinylpyrrolidone (PVP) is used in the preparation of a Vitamin D/calcium phosphate granulation. The polyethylene glycol that is mentioned by Andoh as "equivalent" to PVP is PEG 6000 which is quite different from the PEG 300 -1500 which are the PEGs of claim 1.

Tovey mentions PEG but does not specify the molecular weight of the type of PEG that could be used.

Remington provides a general description of tabletting excipients and binders but does not address the specific problems involved when a calcium salt and Vitamin D are formulated into a pharmaceutical composition.

In the development of the claimed product, the applicants were unable to make a usable product using PVP, PEG 6000, mannitol, maltodextrin alone or in combination with croscarmellose Na under wet conditions.

The cited prior art does not make obvious the claimed composition and for these reasons, it is requested that this ground of rejection be withdrawn.

Claim 19 (added in the Amendment mailed on December 2, 2002) points out a preferred amount of Vitamin D and calcium salt which is disclosed in the Examples of the present application. This composition is not suggested in the prior art of record and it is clearly patentable because of the total amount of Vitamin D and calcium, as well as the ratio of these components.

Since the prior art of record fails to make the claimed subject matter obvious, each ground of rejection should be reversed and patent protection allowed to the inventor's unobvious contribution to the art.

Respectfully submitted,

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(9) Appendix - Claims on Appeal

1. A pharmaceutical composition which consists essentially of Vitamin D, and a calcium salt, as active principles and a binding agent selected from the group consisting of propylene glycol, a polyethylene glycol of molecular weight between 300 and 1500, liquid paraffin and silicone oil, said Vitamin D being present in an amount of 500-1000 I.U. of Vitamin D and said calcium salt being present in a ratio of 1- 2 g of calcium, calculated as elemental calcium, for each 500-1000 I.U. of Vitamin D.

2. A pharmaceutical composition according to Claim 1, in which the calcium used is in the form of a salt selected from the group consisting of phosphate, glycerophosphate, carbonate, bicarbonate, lactate, citrate, tartrate, gluconate and chloride.

3. Pharmaceutical composition according to Claim 1, in which the calcium salt is calcium phosphate.

4. Pharmaceutical composition according to Claim 3, wherein the calcium phosphate is 30-80% by weight calculated on the total composition.

5. Pharmaceutical composition according to Claim 1, in which the Vitamin D used is Vitamin D_2 (or ergocalciferol), Vitamin D_3 (or cholecalciferol), or one of their mixtures.

6. Pharmaceutical composition according to Claim 5, in which the vitamin used is Vitamin D_3.

7. A pharmaceutical composition in a sachet dosage form according to Claim 1, containing the propylene glycol in a quantity comprised between 5-15% by weight calculated on the total composition.

8. A pharmaceutical tablet according to Claim 1, containing liquid paraffin or silicone oil.

9. A pharmaceutical composition in a sachet dosage form characterized as follows:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100,000 IU/g	0.008 g
(corresponding to 800 IU)	
Propylene glycol	0.800 g
Sunset Yellow	0.002 g
Colloidal silica	0.120 g
Lemon flavoring	0.100 g
Microcrystalline cellulose- MCC	0.200 g
Sodium saccharin	0.015 g
Anhydrous citric acid	0.165 g
Sucrose monopalmitate	0.120 g
Mannitol q.s. to	7.000 g

10. A pharmaceutical composition in a sachet dosage form characterized as follows:

Tribasic calcium phosphate	3.100 g
(corresponding to 1200 mg of Ca^{++})	
Cholecalciferol (Vit. D_3) 100,000 IU/g	0.008 g
(corresponding to 800 IU)	

Polyethylene glycol	0.800 g
Sunset Yellow	0.002 g
Colloidal silica	0.120 g
Lemon flavoring	0.100 g
Microcrystalline cellulose- MCC	0.200 g
Sodium saccharin	0.015 g
Anhydrous citric acid	0.165 g
Sucrose monopalmitate	0.120 g
Mannitol q.s. to	7.000 g

11. A pharmaceutical composition in a tablet dosage form characterized as follows:

Tribasic calcium phosphate (corresponding to 1200 mg of Ca^{++})	3.100 g
Cholecalciferol (Vit. D_3) 100,000 IU/g (corresponding to 800 IU)	0.008 g
Liquid paraffin	0.500 g
Sodium carboxymethyl cellulose	0.050 g
Sodium saccharin	0.015 g
Orange flavoring	0.100 g
Sorbitol q.s. to	4.400 g

12. A pharmaceutical composition in a tablet dosage form characterized as follows:

Tribasic calcium phosphate (corresponding to 1200 mg of Ca^{++})	3.100 g
Cholecalciferol (Vit. D_3) 100,000 IU/g (corresponding to 800 IU)	0.008 g
Silicone oil	0.500 g
Sodium carboxymethyl cellulose	0.050 g
Sodium saccharin	0.015 g

Orange flavoring	0.100 g
Sorbitol q.s. to	4.400 g

13. A process for the preparation of a pharmaceutical composition according to Claim 1, characterized by the following steps:
a) In a granulator turning at high speed, distributing a binding agent, consisting of propylene glycol or low molecular-weight polyethylene glycols over a calcium salt;
b) Adding colloidal silica, approximately 25% of mannite, citric acid, and sodium saccharin, and mixing for an appropriate time and at an appropriate speed to produce a first mixture;
c) Adding a second mixture, prepared separately, consisting of sucrose palmitate, a suspending agent, flavoring, a coloring agent, approximately 75% of the mannite and the Vitamin D_3, and mixing together with the first mixture to form a granulate; and
d) Distributing the granulate thus obtained into sachets.

14. A process for the preparation of a pharmaceutical composition according to Claim 1, characterized by the following steps:
a) In a granulator turning at high speed, placing a binding agent, consisting of liquid paraffin or silicon oil, over a calcium salt;
b) Adding in order, to a mixture of colloidal silica, carboxymethyl cellulose and sodium saccharin previously sifted, the Vitamin D_3 and sorbitol, mixing thoroughly every time before a new ingredient is added, and pouring the mixture into the rotating granulator and mixing for

an appropriate time and at an appropriate speed to form a granulate; and
c) Compressing the granulate to a required weight to obtain tablets.

15. Composition According to Claim 1, for use in the treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral fractures and other non-vertebral fractures.

16. Composition According to Claim 1, for use in the prevention of osteoporosis induced by treatment with corticosteroids.

17. Method for treatment of nutritional deficiency of calcium and Vitamin D in the elderly, to reduce the loss of bone tissue linked to age and to prevent femoral fractures and other non-vertebral fractures, in which therapeutically effective quantities of a composition according to Claim 1 are administered to the patient.

18. Method according to Claim 16 for the prevention of osteoporosis induced by treatment with corticosteroids.

19. A pharmaceutical composition as defined in Claim 1, wherein the ratio of vitamin D to calcium salt is 800 I.U. of vitamin D for each 1.2 g of calcium salt, calculated as elemental calcium.